2 SUMMARY

This study investigated the feasibility of using sulfobutylether-β-cyclodextrin (Captisol™), a solubilizing compound manufactured by CyDex, to obtain a 600 mg dose of linezolid in 100 mL or less. The clinical and market formulation for Linezolid Injection is a 2 mg/ml sterile solution of linezolid citrate-buffered at pH 4.8. This formulation is packaged in 100, 200 and 300 ml Excel® infusion bags. These large volumes can be problematic for patients with a history of hypertension, cardiac and/or renal problems. In addition, large volume parenterals are typically more expensive, more difficult to manufacture and more difficult to handle in the clinic when compared to small volume parenterals packaged in glass vials or ampules.

The saturation solubility of linezolid at ambient conditions is 2.9 ± 0.1 mg/ml. The solubility of linezolid was measured in 1, 5, 10, 15, 25 and 50% aqueous Captisol™ solutions and found to be 4.3, 9.5, 15.9, 22.1, 33.4 and 59.9 mg/ml, respectively.

The slowest degradation rate of linezolid in constant ionic strength citrate-phosphate buffers (0.5 M) was between pH 4 to pH 4.8, with Captisol™ having no significant effect on the degradation rate profile. However, it was visually noted that the solutions without Captisol™ turned yellow to amber color much faster than solutions with Captisol™. Further testing at 70°C showed that the chemical stability of linezolid was not significantly affected by the presence of Captisol™ (5% and 10%) in typical formulations consisting of isotonic, 10 mM citrate buffer solutions at pH 4.5. An isotonic formulation consisting of 8 mg/ml linezolid in 10% Captisol™ (75 ml/dose) was physically stable at 25°C and at a refrigerated temperature for the duration of the study, i.e., 2 months. A cost analysis of possible formulations showed that this formulation would range between $5.75 and $10 per 600 mg dose (excluding costs for terminal heat sterilization), primarily due to the high cost of Captisol™ (currently $1000/kg).

This study showed that Captisol™ improved the solubility of linezolid sufficiently to prepare 600 mg doses in volumes less than 100 ml. Also, Captisol™ had no significant effect on the degradation rate profile of linezolid or in the appearance rate of degradation impurities. This study did not address Captisol™ safety or blood compatibility of the formulations. It remains to be determined if the advantages of low volume and photodegradation protection offsets the disadvantage of increased cost of goods.